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PATENT
Atty. Docket No. 104914127

IN THE UNITED STATES PATENT AND TRADEMARK OFFICE

APPLICANTS: Leiden et al.

SERIAL NUMBER: 09/473,830 ART UNIT: 1633

FILING DATE: 12/28/99 EXAMINER: Chen, S.

TITLE: Efficient and Stable In Vivo Gene Transfer to Cardiomyocytes Using Recombinant Adeno-Associated Virus Vectors

CERTIFICATE OF FACSIMILE TRANSMISSION

I hereby certify that this correspondence is being transmitted to the Assistant Commissioner for Patents, Washington, D.C. 20231, by facsimile transmission to telephone number 703-308-4242 on this 2nd day of January, 2002.

1/2/02
Date of Signature

Laura A. Labier

RESPONSE

Commissioner for Patents
Washington, D.C. 20231

Sir:

In response to the Office Action mailed August 29, 2001, in connection with the above-identified application, Applicants submit the following Response. A petition for a two-month Extension of Time for Response, up to and including January 29, 2002, is submitted herewith with an authorization to charge to required fee.

No claims are amended, canceled or added in the present Response.

The Real Party in Interest

The real party in interest in the present application is the assignee of the inventors' rights in the invention, Boston Scientific Corporation.

Related Appeals and Interferences

None.

Status of Claims

Claims 24-46 are pending in the application, and all claims stand rejected under 35 U.S.C. §112, first paragraph, for lack of enablement.

Status of Amendments

All amendments have been entered.

Summary of the Invention

The claimed invention, as currently and most broadly claimed (claim 24), is directed to:

> A method of introducing a nucleic acid encoding a desired molecule into cardiomyocytes which comprises infusing a recombinant adeno-associated virus (AAV) vector into a coronary artery or a coronary sinus for a time and in an amount sufficient to stably and efficiently transduce cardiomyocytes perfused by said artery or said sinus, wherein said AAV vector comprises at least one nucleic acid operably linked to a control region, said nucleic acid encoding said desired molecule.

Although the invention may be used for many purposes, including transducing explanted and perfused hearts and gene therapy of cardiomyocytes *in situ* and *in vivo*, these potential uses are not part of the claims and do not serve as limitations. Rather, the claimed invention is directed to a method of introducing a nucleic acid into cardiomyocytes using a recombinant AAV vector which is infused into a coronary artery or a coronary sinus. Whether the

cardiomyocytes, and coronary artery or coronary sinus are *ex vivo* or *in vivo* is irrelevant (see, *e.g.*, claim 40).

The method is based upon the discovery and demonstration that infusion of these AAV vectors into a coronary artery or coronary sinus can lead to transduction of cardiomyocytes. Prior to the present invention, it had never been demonstrated that such vectors could cross from the coronary artery or coronary sinus into cardiomyocytes at levels sufficient to cause biologically meaningful transduction.

Issues Presented

(1) Whether applicants are only entitled to a scope of protection equal to the working examples in the disclosure, or whether the pending claims are enabled in accordance with 35 U.S.C. § 112, first paragraph, by a disclosure which describes each element of the claimed invention and includes working examples demonstrating the operability of the claimed invention.

(2) Whether applicants are required to enable every utility of the invention, including unclaimed limitations read into the claims from the specification, or whether the pending claims are enabled in accordance with 35 U.S.C. § 112, first paragraph, by a disclosure which describes each element of the claimed invention and includes working examples demonstrating the operability of the claimed invention.

Grouping of the Claims

As the Examiner has presented a single grounds for rejection of the claims, it is believed that the claims stand or fall together.

Argument

The Examiner rejected claims 24-46 under 35 U.S.C. § 112, first paragraph, as failing to meet the enablement requirement, and on the grounds that the scope of the claims is not commensurate with the scope of the enabling disclosure. In particular, the first paragraph of Section 3 of the Office Action suggests that:

> [T]he specification, while being enabling for a method of transducing explanted and perfused hearts of C57BL/6 mice with 1.5x19E9[1] IU of AAV/CMV-lac-Z for 15 minutes via catheter in the left common carotid artery, does not reasonably provide enablement for a method of introducing a nucleic acid encoding any desired molecule into cardiomyocytes by infusing a recombinant AAV vector into a coronary artery or a coronary sinus for any period of time in any amount sufficient to stably and efficiently transduce cardiomyocytes perfused by said artery or sinus in order to facilitate gene therapy approaches for a variety of cardiovascular diseases and conditions, wherein said AAV vector comprises at least one nucleic acid operably linked to a control region.

The second paragraph of Section 3 of the Office Action describes the subject matter covered by the claims with partial accuracy but does not offer any reasons for the rejection.[2] The third paragraph of section 3 of the Office Action describes the working example at pages 10-11 of the specification with partial accuracy but does not offer any reasons for the rejection.

The fourth paragraph of Section 3 of the Office Action quotes two passages from the specification which state that the present invention "facilitates gene therapy approaches for a variety of cardiovascular diseases and conditions" and that the "invention is directed to a method

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[1] This appears to be a typographical error, in which 1.5x10E9 was intended. The figure 1.5x10E9 appears in the working example at page 10, line 19 of the specification.

[2] This paragraph omits any mention of claim 40, and refers to an infusion of 1x10E6 IU AAV/g of body weight when, presumably, 6x10E7 IU AAV/g is intended (as in claims 36 and 39). This paragraph also suggests that claims 41-46 specify the desired molecule when, in fact, claims 41-44 relate to the desired molecule, and claims 45 and 46

of treating a cardiovascular condition." This paragraph then concludes with the statement (emphasis in original):

> Although the new claims have been rewritten to "a method of introducing a nucleic acid encoding a desired molecule into cardiomyocytes by infusing a recombinant AAV vector into a coronary artery or a coronary sinus", the claims still read on *in vivo* **gene therapy** for a variety of cardiovascular diseases and conditions in light of the specification as discussed above.

The fifth, sixth and seventh paragraphs argue that the specification has not enabled gene therapy based upon various alleged uncertainties in the art. However, these paragraphs do not address the enablement of the claimed invention.

The Office Action concludes with a statement that no claim is allowed without addressing the enablement of the claimed invention.

(1) The Claimed Invention is Enabled

As quoted above, the first paragraph of section 3 of the Office Action asserts that the specification is enabling only for the method described in the working example shown on pages 10-11 of the specification and, by implication, suggests that the remainder of the specification enables no additional scope of invention, but does not offer any reasoned explanation why the methods demonstrated to be operable in the working example would not be enabled for the scope of the claims.

In particular, the Office Action acknowledges that the specification is enabling for "transducing explanted and perfused hearts of C57BL/6 mice", but does not offer any

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relate, respectively, to the condition of the individual in which the cardiomyocytes are located and the effect of the desired molecule.

explanation why one of ordinary skill in the art would not be able to perform the method of the invention with human or other mammalian hearts *ex vivo* or *in vivo*. Similarly, the Office Action acknowledges that the specification is enabling for transduction with 1.5x10E9 IU/g of recombinant AAV vector, but does not offer any explanation why one of ordinary skill in the art would not be able to perform the method of the invention with other titers of vector, including the specifically claimed ranges of about 1x10E5 to 1x10E9 IU/g (claims 31 and 34), or about 1x10E6 to 1x10E8 IU/g (claims 32 and 35), or about 6x10E7 IU/g (claims 33, 36 and 39). Similarly, the Office Action acknowledges that the specification is enabling for transduction with the AAV/CMV-lacZ vector, but does not offer any explanation why one of ordinary skill in the art would not be able to perform the method of the invention with AAV vectors including any desired nucleic acids other than the lacZ insert (claim 24), including the specifically claimed nucleic acids encoding an anti-sense RNA or a protein (claim 41); an ion channel gene, a contractile protein, a phospholamban, a β adrenergic receptor, a β adrenergic kinase, a growth factor, an angiogenic factor, a protein or nucleic acid capable of inducing angiogenesis, or a protein or nucleic acid capable of inhibiting angiogenesis (claim 42); FGF-1, FGF-2, FGF-5, VEGF, or HIF-1 (claim 43); or thymidine kinase, p21, p27, p53, Rb or NF-κB (claim 44). Finally, the Office Action acknowledges that the specification is enabling for transduction by infusion "for 15 minutes via catheter in the left common carotid artery," but does not offer any explanation why one of ordinary skill in the art would not be able to perform the method of the invention with infusion into a coronary artery or coronary sinus (claim 24) for any other period, including the specifically claimed periods of at least about 2 to 30 minutes (claims 28 and 34), about 5 to 20 minutes (claims 29 and 37), or about 15 minutes (claims 30, 38 and 39).

In order to make an enablement rejection, the Examiner has the initial burden to establish a reasonable basis to question the enablement provided for the claimed invention. *In re Wright*, 999 F.2d 1557, 27 USPQ2d 15 10 (Fed. Cir. 1993) (Examiner must provide a reasonable explanation as to why the scope of protection provided by a claim is not adequately enabled by the disclosure). As stated by the court in *In re Marzocchi*, 439 F.2d 220, 169 USPQ 367 (CCPA 1971), "it is incumbent upon the Patent Office, whenever a rejection on this basis is made, to explain it doubts the truth or accuracy of any statement in a supporting disclosure and to back up assertions of its own with acceptable evidence or reasoning which is inconsistent with the contested statement. Otherwise, there would be no need for the applicant to go to the trouble and expense of supporting his presumptively accurate disclosure." 169 USPQ at 370. MPEP 2164.04]

The Office Action does not meet this burden. Rather, the Office Action merely recites the scope of the claimed invention, points out that the claimed invention reads on unclaimed subject matter (*i.e.*, gene therapy), and then argues that the unclaimed subject matter is not enabled. Therefore, the rejection is improper.

Moreover, an analysis of an enablement rejection requires a determination of whether the disclosure, when filed, contained sufficient information regarding the subject matter of the claims as to enable one skilled in the pertinent art to make and use the claimed invention. The test of enablement is whether one skilled in the art could make or use the claimed invention from the disclosures in the patent application coupled with information known in the art without undue experimentation. *United States v. Telectronics, Inc.*, 857 F.2d 778, 8 USPQ2d 1217 (Fed. Cir. 1988); *In re Stephens*, 529 F.2d 1343, 188 USPQ 659 (CCPA 1976). A patent need not teach,

and preferably omits, what is well known in the art. *Spectra-Physics, Inc. v. Coherent, Inc.*, 827 F.2d 1524, 3 USPQ2d 1737 (Fed. Cir. 1987). Determining enablement is a question of law based on underlying factual findings. *In re Vaeck*, 947 F.2d 488, 495, 20 USPQ2d 1438, 1444 (Fed. Cir. 1991); *Atlas Powder Co. v. E.I. du Pont de Nemours & Co.*, 750 F.2d 1569, 224 USPQ 409 (Fed. Cir. 1984). MPEP 2164.01.]

The Office Action makes no factual findings that suggest that the claimed subject matter is not enabled. Rather, as noted above, the Office Action merely recites the scope of the claimed invention, points out that the claimed invention reads on unclaimed subject matter (*i.e.*, gene therapy), and then argues that the unclaimed subject matter is not enabled. Therefore, the rejection is improper.

Thus, for at least the foregoing reasons, Applicants submit that the rejections are improper as a matter of law and should be withdrawn.

(2) Enablement of Unclaimed Subject Matter

The Office Action states that "[a]lthough the new claims have been rewritten to 'a method of introducing a nucleic acid encoding a desired molecule into cardiomyocytes by infusing a recombinant AAV vector into a coronary artery or a coronary sinus' the claims still read on *in vivo* gene therapy", and then proceeds to argue against the enablement of gene therapy. Thus, in short, the Examiner has decided to ignore the claimed subject matter and to base enablement rejections on unclaimed subject matter. This is not consistent with the law.

Claims may read on much subject matter that is unclaimed, and may still be enabled. Merely as an example, a claim to a screw may read on a perpetual motion machine which

comprises a screw (in combination with other parts). The claim to the screw may nonetheless be enabled even if the unclaimed perpetual motion machine cannot be. Similarly, irrespective of whether the present specification enables gene therapy (which, Applicants submit, it does), the claims to methods of transducing cardiomyocytes are enabled irrespective of the Examiner's beliefs regarding enablement of gene therapy.

Therefore, in light of the foregoing reasons, Applicants respectfully request that the rejections under 35 U.S.C. § 112, first paragraph, be reconsidered and withdrawn.

SUMMARY

Claims 24-46 are pending in the application.

Applicants request that the Examiner reconsider the application and claims in light of the foregoing Response, and respectfully submit that the claims are in condition for allowance. If, in the Examiner's opinion, a telephonic interview would expedite the favorable prosecution of the present application, the undersigned attorney would welcome the opportunity to discuss any outstanding issues, and to work with the Examiner toward placing the application in condition for allowance.

A petition for a two-month Extension of Time for Response is submitted herewith. The Commissioner is hereby authorized to charge the fee for the petition, and any other fees now required to maintain the pendency of the application, to Deposit Account No. 08-0219.

Respectfully submitted,
Hale and Dorr, LLP

January 2, 2002

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CLAIM APPENDIX
(CLAIMS AS PENDING AFTER 6/13/01 PRELIMINARY AMENDMENT)

24. A method of introducing a nucleic acid encoding a desired molecule into cardiomyocytes which comprises:

infusing a recombinant adeno-associated virus (AAV) vector into a coronary artery or a coronary sinus for a time and in an amount sufficient to stably and efficiently transduce cardiomyocytes perfused by said artery or said sinus, wherein said AAV vector comprises at least one nucleic acid operably linked to a control region, said nucleic acid encoding said desired molecule.

25. The method of claim 24, wherein said AAV transduces at least about 10% of said cardiomyocytes.

26. The method of claim 24, wherein said AAV transduces at least about 40% of said cardiomyocytes.

27. The method of claim 24, wherein said AAV transduces at least about 50% of said cardiomyocytes.

28. The method of claim 24, wherein said AAV is infused for at least about 2 minutes to about 30 minutes.

29. The method of claim 24, wherein said AAV is infused for at least about 5 minutes to about 20 minutes.

30. The method of claim 24, wherein said AAV is infused for about 15 minutes.

31. The method of claim 24, wherein said amount of AAV is about 1 x 10^5 IU AAV per gram body weight to about 1 x 10^9 IU AAV per gram body weight.

32. The method of claim 31, wherein said amount of AAV is about 1 x 10^6 IU AAV per gram body weight to about 1 x 10^8 IU AAV per gram body weight.

33. The method of claim 32, wherein said amount of AAV is about 6 x 10^7 IU AAV per gram body weight.

34. The method of claim 24, wherein about 1 x 10^5 IU AAV per gram body weight to about 1 x 10^9 IU AAV per gram body weight is infused for about 2 to about 30 minutes.

35. The method of claim 34, wherein about 1 x 10^6 IU AAV per gram body weight to about 1 x 10^8 IU AAV per gram body weight is infused.

36. The method of claim 35, wherein about 6 x 10^7 IU AAV per gram body weight is infused.

37. The method of any one of claims 34, 35 or 36, wherein said AAV is infused for about 5 to about 20 minutes.

38. The method of any one of claims 37, wherein said AAV is infused for about 15 minutes.

39. The method of claim 34, wherein about 6 x 10^7 IU AAV per gram body weight is infused for about 15 minutes.

40. The method of claim 24, wherein said coronary artery is infused *ex vivo* or *in vivo*.

41. The method of claim 24, wherein said desired molecule is an anti -sense RNA or a protein.

42. The method of claim 24, wherein said desired molecule is an ion channel gene, a contractile protein, a phospholamban, a β adrenergic receptor, a β adrenergic kinase, a growth factor, an angiogenic factor, a protein or nucleic acid capable of inducing angiogenesis, or a protein or nucleic acid capable of inhibiting angiogenesis.

43. The method of claim 24, wherein said desired molecule is FGF-1, FGF-2, FGF-5, VEGF, or HIF-1.

44. The method of claim 24, wherein said desired molecule is thymidine kinase, p21, p27, p53, Rb or NF-κB.

45. The method of claim 24, wherein said cardiomyocytes are in an individual having a vascular condition selected from the group consisting of restenosis, atherosclerosis, congestive heart failure, ischemic cardiomyopathy, malignant arrhythmia, myocardial infarction, congestive heart failure, and dilated and hypertrophic cardiomyopathy.

46. The method of claim 24, wherein said desired molecule has an effect selected from the group consisting of inducing angiogenesis, inhibiting angiogenesis, stimulating or inhibiting cell proliferation, treating restenosis, treating atherosclerosis, treating congestive heart failure, treating ischemic cardiomyopathy and treating malignant arrhythmia.